said fungal cell culture supernatant with sera from a test subject; and determining the serum antibody level of said test subject.--

REMARKS

Reconsideration is requested.

Claims 47-53 have been added. Claims 1-12 and 30-53 are pending. Claims 1-12 have been withdrawn from consideration. Claims 30-53 are under active consideration.

Claim 30 has been amended and new claims 47-51 have added in response to the Examiner's comments specifically at the end of the last paragraph on page seven of the Office Action of July 18, 2002 (Paper No. 8). Support for the amendments may be found, for example, on pages 14 and 16 of the specification. No new matter has been added. Support for claims 52 and 53 may be found in the description relating to results presented in Table 10 on page 30 of the specification. No new matter has been added.

The Section 112, first paragraph, rejection of claim 45 is traversed. Reconsideration and withdrawal of the rejection are requested.

The Examiner asserts that the specification fails to teach how to formulate the claimed vaccines. The claimed vaccines contain cell cultures and formulation of the same is not believed to place an undue burden on one of ordinary skill in the art. The applicants have demonstrated vaccination of mice in the present specification and the Examiner's apparent requirement for results which may be required by a regulatory agency is not an appropriate standard. The Examiner's requirement for demonstration of a "protective immunity to a fungal yeast infection or disease induction" (see, page 3

of Paper No. 8) would not be required by one of ordinary skill in the art. In this regard, the Examiner is requested to see her own reference (Deepe, Clinical Microbiology Reviews, Oct. 1997, pages. 585-596) which states that "although vaccination and immunization often are used interchangeably, they have, strictly speaking, different meanings. Vaccination does not necessarily produce immunization. The two words are synonymous when vaccination leads to an immunization against infection. The term "immunization" is used herein when it is clear that a vaccine induces a protective response." See, Deepe, page 585, right column, first paragraph. Accordingly, the term "vaccine" may not necessary encompass the ability of a specific antigen to induce protective immunity.

As for the Examiner's comment relating to the statement in the specification that variation was demonstrated (see, page 3 of Paper No. 8 and page 17 of the specification), variation demonstrated with different fungi by the applicants will not produce an undue burden on one of ordinary skill in the art and, in fact, provides more detailed source of guidance for making and using the claimed invention. As for the Examiner's concern over an alleged lack of teaching with regard to dosages, the applicants note that one of ordinary skill in the art may easily titrate dosages, without undue experimentation being required. Again, the applicants submit, with all due respect, that enablement does not require demonstration of safety and efficacy as may be required by the FDA.

As for the Examiner's cited references, the applicants note that Otcenasek (Vet Med (Praha) 1981, April 1981 26(4): 193-202 (abstract only)) specifically states that "mycosis can be successfully controlled by vaccination." Moreover, the abstract

characterizes the entirety of the paper as "deal[ing] with the theoretical problems of the nature and duration of immunity to these diseases and with the choice of the best vaccines and vaccination procedures" (emphasis added). Accordingly, the cited reference appears to discuss opportunities for optimizing vaccination as opposed to demonstrating that it would be unreasonable to use vaccination or that use of vaccination would require undue experimentation.

As for the Examiner's citation of Deepe, the above-noted comments contradict the Examiner's reliance on the reference. Moreover, Deepe was published, as a review article, in 1997, three years before the applicant's priority filing, and without benefit of reviewing the present specification. More importantly perhaps, the applicants note that page 586 of Deepe, specifically referred to by the Examiner, states in the left-hand column that "despite the failure of vaccine for coccidioidomycosis, there are useful fungal vaccines in veterinary medicine" (emphasis added). It is not unreasonable therefore to believe that vaccines may be developed for humans.

The Examiner's comments relating to motifs or canonical sequences and genes or gene products discussed in Deepe (see, page 4 of Paper No. 8) are not understood as the presently claimed invention involves supernatants as opposed to specific proteins, motifs, genes or gene products. Finally, the applicants note that Deepe provides encouraging results on pages 587-588, as well as Table 1 on page 589.

As for the Examiner's review of factors he considered in determining whether undue experimentation is required, as described In re Wands (8 USPQ 2d 1400), the applicants note that the specification demonstrates an undue amount experimentation would not be required. As noted above, vaccine formulations are well-known in the art and they do not require undue experimentation. Specifically, the applicants have shown that, for example, 2 mg antigen /0.1 ml saline given intra-peritoneally to mice provides an antibody response. Moreover, without being held to any specific mechanistic theory, the applicants believe that an antibody response to fungi prevents, or at least reduces, infection in at least two ways. In the first manner, antibodies adhere to the fungal surface, preventing it from adhering to the host-target site. In a second mechanism, antibodies activate the complement system which form an insertion protein complex

which produces holes in the fungal membrane. One of ordinary skill in the art will appreciate these mechanisms and find the evidence presented in the specification to be enabling to produce and use the presently claimed invention, without undue experimentation.

Withdrawal of the Section 112, first paragraph, rejection of claim 45 is requested.

The Section 102 rejection of claims 30-36, 40-41 and 45-46 over Pasarell (Journal of Clinical Microbiology, July 1990, pages 1655-1657) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner's comments noted at the bottom of page 7 of Paper No. 8 have been noted and the claims amended, without prejudice, to recite distinguishing features over the cited art. Support for the amendments may be found in the above-noted passages of the specification. Reconsideration and withdrawal of the rejection are requested.

The Section 102 rejection of claims 30-35, 41 and 46 over Calera (Infection and Immunity, June 1994, pages 2322-2333) is traversed. Reconsideration and withdrawal of the rejection are requested. Again, the applicants note that the claimed invention requires features not found in the cited art. The applicants disagree with the Examiner's characterization of certain of the claim recitation do not define over the cited art. Specifically, the applicants have demonstrated that subjecting the supernatant to freezing produces a different product. See, page 17, first paragraph of the specification. Accordingly, the Examiner's comments spanning pages 9-10 of Paper No. 8 are not believed to be correct in view of the evidence provided in the specification. Reconsideration and withdrawal of the Section 102 rejection of claims 30-35, 41 and 46 over Calera are requested.

The Section 102 of claims 30-35, 37-39, 41 and 45-46 over Takesako (U.S. Patent No. 6,333,164) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The fungal antigens of the cited reference appear to be proteins. The applicants have demonstrated in their specification at page 16, last paragraph, that protease

digestion of the claimed supernatants had a minor affect on the antigens of the claimed invention. Accordingly, the supernatants of the presently claimed invention are different from the cited art and the cited patent fails to teach each and every aspect of the presently claimed invention. The Examiner will appreciate in this regard that Takesako appears to use "insoluble fractions containing cytoplasmic membrane proteins" (see, column 6, lines 65-67) to produce components wherein cell wall-constituents, such as "mannan or glucan" may be removed. See, column 11, line 66 to column 12, line 1 of Takesako. That is, the applicants believe Takesako specifically selected for insoluble antigens which are different from the soluble supernatant antigens of the presently claimed invention.

The applicants further note that Takesako appears to have enhanced immunogenicity of their preparations by using immunostimulants such as Freund's incomplete adjuvant and cholera toxin, which were not required by the presently described methods.

The Examiner's statement that Takesako suspended fungal antigens in Potato-Dextrose medium and subjected the same to shaking overnight, is not believed to be a correct reading of Takesako. In fact, the applicants believe that the fungal cells that served as the source of the insoluble antigens of Takesako were suspended in Potato-Dextrose medium. As noted above, these insoluble antigens of Takesako are quite different from the presently claimed invention.

Withdrawal of the Section 102 rejection of claims 30-35, 37-39, 41 and 45-46 over Takesako is requested.

The Section 102 rejection of claims 30-41 and 45-46 over Manning (The Laryngoscope, 108, October 1998), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The cited references teaches, at best, the use of cells, as opposed to supernatants from cell cultures, as claimed, which are discarded according to the teachings of the cited reference. Specifically, the cell preparations were "harvested by filtration, defatted with acetone, and lyophilized." See, page 14-89, right column, materials and methods, fourth paragraph. Beyond this processing, the applicants note

that the characteristics of the presently claimed supernatants are adversely effected by lyophilization, as demonstrated in the present specification and noted above. Accordingly, the Examiner's comments with regard to certain recitations of the claims relating to temperature treatment, are a distinctive feature of the presently claimed invention which defines over the cited art. Moreover, the compositions of Manning are not the same as the presently claimed invention and cannot anticipate the same.

Withdrawal of the Section 102 rejection of claims 30-41 and 45-46 over Manning is requested.

The Section 102 rejection of claims 30-34, 41, 44 and 46 over Malling (Allergy, 1986, 41, 57-67), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

Malling only teaches the use of a commercial product which is uncharacterized and hence comparison is not possible between the presently claimed invention and the "lyophilised, partially purified and standardized preparation of *Cladosporium herbarum*" which was purchased from Pharmacia. See, page 58, right column, first full paragraph of Malling. The applicants note however that the lyophilised product used by Malling will not be the same as the presently claimed invention as the applicants have demonstrated that lyophilization or freezing produces a product which is functionally different from the presently claimed invention. See, page 17 of the present specification. While the applicants understand that the Patent Office does not have the facilities for examining and comparing the presently claimed invention with the cited art, as is often noted by the Examiner in Paper No. 8, the fact that Malling uses a lyophilised product and the applicants have demonstrated that lyophilization changes the character of the supernatants, necessarily supports the applicants' belief that the Examiner has failed to demonstrate that the cited art literally or inherently teaches the presently claimed invention. Accordingly, the Section 102 rejection of claims 30-34, 41, 44 and 46 over Malling should be withdrawn.

The Section 102 rejection of claims 30-36, 41-42 and 45-46 over van der Heide (Allergy, 1985, 40, 592-598), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the fact that van der Heide teaches the use of

mycelial antigens or, more specifically "somatic antigens(M)" (see, page 595, bottom of right column and page 696, top of left column) which will be recognized as excluding supernatant antigens, as are included in the presently claimed invention.

Withdrawal of the Section 102 rejection of claims 30-36, 41-42 and 45-46 over van der Heide is requested.

In view of the above, the claims are submitted to be in condition for allowance and a Notice to that affect is requested along with return of an initialed copy of the attached PTO-1449 Form. The attached RCE is being filed so that the references listed in the attached PTO-1449 Form, also attached, may be considered and made of record.

The applicants note that claim 43 does not appear to have been rejected in Paper No. 8 and, at a minimum, allowance of the same in the Examiner's next Action is requested.

The Examiner is requested to contact the undersigned if anything further is required in this regard.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

B. J. Sadoff
Reg. No. **36,663**

1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

VERSION OF MARKINGS TO SHOW CHANGES MADE

30. (Amended) A fungal or yeast cell culture supernatant as antigenic source for detecting level of antibodies from a sample test subject, said fungal cell culture supernatant containing fungal components shed into the supernatant during culturing.

43. (Amended) [The] A fungal cell culture supernatant of *Bipolaris* displaying antigenicity towards antibody detection in a serodiagnostic assay for fungal antibody which comprises preparing said *Bipolaris* fungal cell culture supernatant; reacting said fungal cell culture supernatant with sera from a test subject; and determining the serum antibody level of said test subject.

46. (Amended) A fungal or yeast cell culture supernatant consisting essentially of [comprising only partially] of nucleic acids or proteins.